UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,549	05/02/2002	Dan L. Eaton	P3230R1C001-168	9996

20995 7590 07/19/2006

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,549	EATON ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6-28-06 has been entered.

The amendment to the claims filed 6-28-06 has been entered into the record. Claims 6-17 are pending and under examination. Claims 1-5 have been cancelled.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Objections/Rejections Withdrawn

The rejection of claims 3-17 under 35 USC 102(e) as being clearly anticipated y Starling et al (WO 01/46260, with priority to US provisional 60/172,025 filed 23 December 1999) or Starling et al (US Patent Application Publication US 2002/0123617) is withdrawn in view of the declaration and arguments of record.

Rejections Maintained

Priority

Applicants argue that the data in Example 18 (tumor versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8-24-00. This is not persuasive, the priority document does not comply with 35 USC § 120, utility and enablement for reasons set forth in the previous office action of record and reasons set forth herein. This relied upon utility is not a substantial utility for reasons made of record and argued herein.

Claims 6-17 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility due to its not being supported by a specific, substantial and credible utility or, in the alternative a well-established utility is maintained for reasons made of record in all the Office Actions and herein.

Applicants' arguments have been carefully considered but are not persuasive. Applicants' discussion of the utility legal standard, burden of proof and standard of proof is acknowledged. However, the présent rejection is based upon Applicants' failure to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Accepting applicants standard of utility would result in a per se rule that any disclosed difference in mRNA expression is significant, relevant, and tumor-dependent and that any such difference would require a per se rule of utility for the polynucleotide, the encoded polypeptide and antibodies thereto. The office declines to attenuate the utility requirement to this degree because this standard is not what the art teaches. The position of the office is two fold: (1) mRNA levels do not correlate with corresponding protein levels and (2) the art clearly teaches that changes in mRNA levels can be either tumor-dependent or tumor-independent. The position is summarized herein. No information is provided in the differential analysis of the PRO mRNA expression regarding the level of expression, activity, or role in cancer of the PRO polypeptide in the instant specification. The specification fails to establish the correlation between the disclosed change in PRO mRNA transcript and a change in PRO polypeptide expression in normal tissue versus tumor tissue. Applicants again rely on an asserted reasonable probability of the correlation of mRNA levels with protein levels. This again is not persuasive, the preponderance of evidence of record establishes that one skilled in the cancer diagnostic art would not find it "more likely than not" that the mRNA levels correspond with the protein levels, see Haynes et al, Pennica et al, Gokman-Polar et al and Lewin et al. Applicants argue the court holdings in *Fujikawa v. Wattanasin*, 93 F3d. 1559, 39 USPQ 2d

1985 (Fed. Cir. 1996) and *Cross v Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed Cir. 1985) that indicate that when the *in vitro* results are general predictable of *in vivo* results establishes a significant probability that in vivo testing for the particular pharmacological activity will be successful. This is not persuasive, there is no claimed pharmaceutical composition and the issue is not correlation of in vitro data with in vivo results. The issue is solely *in vitro*, and the lack of reasonable correlation between mRNA levels and protein levels *in vitro*. In contrast to *Fujikawa v. Wattanasin*, 93 F3d. 1559, 39 USPQ 2d 1985 (Fed. Cir. 1996) and *Cross v Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed Cir. 1985) this specification does not teach *in vitro* data for the protein. No levels of the protein are taught, absolute or not. Applicants review the record and indicate that their rebuttal evidence establishes the "more likely than not" standard for utility. Applicants argue Hu et al does not teach that indicate that a lack of correlation means that genes with a less than five fold change in level of expression in cancer cannot serve as a molecular markers of cancer. Hu et al was cited to provide evidence that one skilled in the art would not more likely than not believe that a change less than five fold would be indicative of a role in cancer as it related to the allegations of utility with respect to therapeutics and gene therapy. In order to have utility for therapeutic purpose or be useful in gene therapy, there must be some correlation with known or disclosed biological activity. Applicants argue data manipulation by Hu et al renders conclusions not reliable. If data manipulation renders conclusions not reliable, as a correlary the data manipulation of the microarray data renders Applicants conclusions not reliable. Applicants argue that Hu et al is limited to the data type for breast cancer cells. This is not persuasive because Hu et al is not the only reference that establishes the lack of correlation of mRNA levels with protein levels. The position of the office is that the art of record indicates that there is no reasonable correlation and that the allegation of utility based upon therapeutics is not specific and substantial. Applicants argue that they have established that the gene encoding the PRO polypeptide is differentially expressed and thus rely again on the "reasonable correlation"

of mRNA expression with protein expression. This again is not persuasive Haynes et al. is cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as **40-fold** or even **50-fold** were not uncommon (pg. 1863) and specifically teach "These results suggests that even for a population of genes predicted to be relatively homogenous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of corresponding mRNA transcript." (page 1863, column 1, section 2.1). Haynes et al teaches "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts. " (see page 1870, column 1, Concluding Remarks). Therefore, the skilled artisan immediately recognizes that, at the time of the invention, that no direct correlation between gene amplification/mRNA levels and increased polypeptide levels exists, no dogma exists between mRNA and polypeptide levels (for which neither are disclosed within the instant specification for PRO). Haynes et al specifically caution about drawing conclusions of protein levels based on transcript levels... indicating that there is no strong correlation. The art specifically teaches that the findings for yeast are also present in humans. Anderson et al teach that "Despite extensive work on the regulation of many individual genes, little attention appears to have been paid to the global question of the relation between mRNA and corresponding cellular protein abundances.." (Anderson et al , Electrophoresis, 18:533-537, 1997; see page 536, column 2.). Anderson et al teach that the correlation is 0.48 and indicates that the two major phages of gene expression regulation are of approximately equal importance in determining the net output of protein. Reanalysis of the data of Kawamoto et al, indicates that the correlation is coefficient is poor when one gene product, well separated from the gene cluster is omitted from the calculation (Anderson et al page 536, column 2, first full paragraph). Further, the lack of correlation between mRNA levels and protein levels in cancer is demonstrated by Chen et al (Molecular and Cellular Proteomics, 1:304-

313, April 2002). Chen et al indicate that "Using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, we showed that only a subset of the proteins exhibited a significant correlation with mRNA abundance." (see Chen et al page 304, column 1, abstract). As such, not all cancer proteins have a correlation and therefore, in the absence of any specific evidence to the contrary with respect to the polypeptide or antibodies that bind them, there is reason to doubt the asserted truth of the assertion of utility. Lian et al (Blood, 98:513-524, 2001) show a similar lack of correlation in mammalian (mouse) cells (see page 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al (J. Biol. Chem., 277:31291-31302, 2002) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (page 31291, abstract). Finally, Greenbaum et al (Genome Biology, 4:117.1-117.8, 2003) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, second column) that primarily because of a limited ability to measure protein abundances, researches have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. As such, the preponderance of the evidence indicates that the state of the art does not provide for a reasonable correlation between mRNA and protein abundances. As previously set forth, given the evidence presented it is clear that one skilled in the art would not assume that a small increase/decrease in mRNA would correlate with corresponding changes in polypeptide levels. In view of the totality of the evidence of record, one skilled in the art would not assume that gene expression (mRNA) necessarily parallels or is predictive of protein expression and would have to perform further experimentation to verify or rule it out. As such, this further experimentation indicates that the asserted utility is not "substantial". It is noted that

the cited literature supports the position of a lack of correlation of gene amplification, mRNA levels and protein expression and specifically cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Differential analysis of mRNA expression is not always correlated with protein levels. For example Allman (Blood, 87(12):5257-68, 1996) disclosed that germinal center B cells express dramatically more BCL-6 than resting B cells, despite similar BCL-6 mRNA levels in the two populations. Page 5257, paragraph bridging left and right columns. MRNA translation is regulated in man genes and can be mediated by binding of proteins to cis-acting RNA motifs in the untranslated regions of the mRNAs (paragraph bridging pages 5266-5267). Furthermore, Haynes et al states that "Interpretation of quantitative mRNA expression profiles frequently implicitly or explicitly assume that for specific genes the transcript levels are indicative of the levels of protein expression" (page 1863, left column) and ".. it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis" (page 1863, right column). In view of the fact that there are numerous levels of control of protein synthesis, degradation, processing, and modification, that are only apparent by direct analysis, the skilled artisan would not know if the disclosed difference in mRNA expression is associated with the corresponding change in the level of protein. Where systematically studied, the art teaches that it is not reasonable to conclude and not more likely than not that the protein levels correspond to the mRNA levels. Hu et al of record also provides teachings that differential analysis of mRNA expression there are biologically relevant results as well as biologically irrelevant results. Furthermore LaBaer (Nat Biotechnol. 21(9):976-7, 2003) teaches that "In the accelerating quest for disease biomarkers, the use of high-throughput technologies, such as DNA microarrays and proteomics experiments, has produced vast datasets identifying thousands of genes whose expression patters differ in disease versus normal samples. Although many of these

differences may reach statistical significance, they are not always biologically meaningful. For example, reports of mRNA or protein changes of as little as two-fold are not uncommon, and although some changes of this magnitude turn out to be important, most are attributable to disease-independent differences between the samples." (page 976, paragraph bridging 2-3 columns). A tumor-independent change in mRNA expression cannot be used as a disease marker. The significance of the reported change in the specification cannot be ascertained because the skilled artisan would not know if the difference in mRNA expression is tumor-dependent or tumor-independent. Even if one were to assume that the present results with PRO mRNA expression could be associated with an assume change in polypeptide expression (a point not conceded by the office), it still could not be ascertained if the difference is disease-dependent or disease-independent because such is not shown for the mRNA levels. It is maintained that the instant claims encompass polypeptides of as yet undetermined function or biological significance. Until some actual or specific significance can be attributed to the claimed polypeptide, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use it. There is no immediately apparent or "real world" utility for the claimed polypeptides as of the instant filing date. After further research, a specific and substantial utility might be found for the polypeptides of the instant invention. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicants invention is incomplete. Applicants argue the Grimaldi declarations. The countervailing evidence shows that the skilled artisan would not know if the disclosed change in PRO transcripts is tumor-dependent or tumor-independent. See Hu and LaBaer, as discussed above. A tumor-independent detection of a change in mRNA expression cannot be used as a tumor marker. The skilled artisan would not know if or how expression of the PRO polypeptide would change in tumors because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis. See Haynes, as discussed above. This conclusion is

supported by: Allman (Blood. 1996 Jun 15;87412):5257-68): germinal center B cells express dramatically more BCL-6 protein than resting B cells, despite similar BCL-6 MRNA levels in the two cell populations'' (page 5257, paragraph bridging left and right columns); Molecular Biology of the Cell, 3rd ed.: other controls can act later in the pathway from DNA to protein to modulate the amount of gene product that is made'' (page 453, last full paragraph); Molecular Biology of the Cell, 4th ed.: the final level of a properly folded protein in a cell therefore depends upon the efficiency with which each of the many steps from DNA to protein) is performed'' (page 363, last full paragraph and page 364, Figure 6-90); Genes V1: the production of RNA cannot inevitably be equated with production of protein'' (paragraph bridging pages 847-848). The declaration of Dr. Polakis under 37 CFR 1.132: ". . . there have been published reports of genes for which such a correlation does not exist, . . .'' (paragraph 6),. Meric (Mol Cancer Ther. 1(11):97 1-9, 2002): Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability. Page 971, left column, first paragraph of introduction. See also the Polakis declaration wherein it is taught that -20% of the samples examined do not show a correlation between an increase in the level of mRNA and an increase in the level of the encoded protein (paragraph 5). Even if one were to assume that the disclosed change in PRO transcripts could reasonably be correlated with an assumed change in PRO polypeptide expression the skilled artisan still would not know if the assumed change in PRO polypeptide expression is tumor-dependent or tumor-independent because it is unknown if the disclosed change in PRO transcripts is tumor-dependent or tumor-independent. Neither the specification nor any of Applicants' arguments, exhibits, declarations or other evidence providing any specific data disclosing if or how the PRO polypeptide expression changes in tumor tissue. Instead, Applicants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO transcripts and PRO polypeptide expression to argue that it is more likely than not that a change in PRO transcripts is

correlated with an assumed change in PRO polypeptide expression. Without any evidence of the expression of PRO polypeptide in tumor tissue or normal tissue this argument is of no avail to Applicants. The asserted utility of the claimed polypeptides would require or constitute carrying out further research to identify or reasonably confirm a ''real world'' context of use. Regarding the requirement for further experimentation as a basis for lack of utility, utilities that require or constitute carrying out further research to identify or reasonably confirm a ''real world'' context of use are not substantial utilities (M.P.E.P. 2107.01 1). In the present case, the asserted diagnostic or therapeutic utilities of the PRO gene, polypeptide and antibodies would require or constitute carrying out further research to identify or reasonably confirm a ''real world'' context of use because the skilled artisan would not know if or how PRO polypeptide expression, or expression of any of the other claimed polypeptides, would change in tumors. Unlike the situations wherein a claimed compound has been tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient under the patent laws, or wherein an invention has only limited utility and is only operable in certain applications and therefore has some degree of utility sufficient for patentability, in the present situation Applicants have not provided any testing of the expression of the PRO polypeptide. In the absence of any information on the role, activity or expression of the PRO polypeptide in cancer, the examiner therefore considers the asserted utilities to not be specific and substantial because the skilled artisan would not know if the reported change in PRO transcripts is tumor-dependent or tumor-independent and would not know if or how PRO polypeptide expression would change in cancer. Although the asserted utility may be specific to the claimed invention, it is not substantial. Therefore, the claimed invention lacks a specific and substantial asserted utility. Applicants' utility standard would mandate only a showing that it is not implausible, that the invention will work for its intended purpose. If mere plausibility were the test for how to use a claimed invention, Applicants could obtain patent rights to "inventions'' based on a disclosure consisting of little more than guesses

as to the likelihood of their success. When one of the guesses later proved true, the "inventor'' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor disclose how to use an invention rather than merely proposing an unproved hypothesis. As set forth in *Brenner v. Manson*: But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. ''(A) patent system must be related to the world of commerce rather than to the realm of philosophy.'' There is a complete absence of data supporting the statements which set forth the desired results of the claimed invention and the countervailing evidence shows that the skilled artisan would not know if the disclosed change in PRO transcripts is tumor-dependent or tumor-independent and would not know if or how expression of the PRO polypeptide would change in tumors. Applicants are not being asked to prove the asserted diagnostic utility either as a matter of statistical certainty or beyond a reasonable doubt. Rather, the facts to be established are, is the reported change in PRO transcripts tumor-dependent or tumor-independent and, if the reported change is tumor-dependent, is there a corresponding change in PRO polypeptide expression. The specification does not establish if the disclosed change in PRO mRNA expression is one of those cases where there is a correlation between mRNA expression and polypeptide expression. Applicants have not provided any testing of PRO polypeptide expression. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO polypeptide, the specification does not provide some immediate benefit to the public for the PRO polypeptide. None of Applicants' exhibits, arguments or declarations establish if or how expression of the PRO polypeptide changes in tumor tissue as compared to normal tissue. Instead, Applicants merely propose a utility that is not implausible, relying on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO

mRNA expression and PRO polypeptide expression without any evidence of the expression level of the polypeptide in tumor tissue or normal tissue. See. e.g., *Brenner,* 383 U.S. at 534, 148 USPQ at 695 (An invention does not have utility sufficient to satisfy 101 until it is refined and developed to the point of providing a specific benefit in currently available form. The following passage from the specification seems most relevant for construing the asserted diagnostic utility. [0336] The PRO polypeptides and nucleic acid molecules of the present invention may also be used diagnostically for tissue typing, wherein the PRO polypeptides of the present invention may be differentially expressed in one tissue as compared to another, preferably in a diseased tissue as compared to a normal tissue of the same tissue type. PRO nucleic acid molecules will find use for generating probes for PCR, Northern analysis, Southern analysis and Western analysis. Page 93. [0407] The anti-PRO antibodies of the invention have various utilities. For example, anti-PRO antibodies may be used in diagnostic assays for PRO, e.g., detecting its expression (and in some cues, differential expression) in specific cells, tissues, or serum. Page 112. [0530] Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. These assays provided the following results. Page 140. The specification does not make a specific assertion regarding positive correlations between PRO mRNA expression and PRO polypeptide expression, i.e., if PRO mRNA is up-regulated, PRO polypeptide is up-regulated or vice versa. The correlation between the disclosed change in PRO mRNA expression and a change in PRO polypeptide expression is unknown and is not disclosed. In fact, Applicants argue that a necessary correlation between gene expression and protein expression is not required to establish utility. The second Grimaldi declaration asserts that: " . . . even in the rare case where the protein expression does not correlate with the

mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.'' Paragraph 6. The Ashkenazi declaration asserts that: "absence of gene product overexpression still provides significant information for cancer diagnosis and treatment.'' Paragraph 6. Applicants are arguing that whatever the expression level and whatever the correlation, the PRO polypeptide is useful because skilled artisans could figure out for themselves what any observed experimental result might mean. The specification does not disclose anything regarding ''more accurate tumor classification.'' The examiner does not agree that such a disclosure provides a specific benefit in currently available form'' because the expression of all polynucleotides or polypeptides in a tumor sample can invariably be classified as either increased, decreased, non-existent, or unchanged as compared to some standard level of expression. It can then be asserted that all proteins or polynucleotides that are expressed in this manner can be used to detect or characterize the tumor. Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific nor a substantial utility. There is a complete absence of data supporting the statements which set forth the desired results of the claimed invention and the countervailing evidence shows that the skilled artisan would not know if the disclosed change in PRO transcripts is tumor-dependent or tumor-independent and would not know if or how expression of the polypeptide would change in tumors. The specification fails to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. Therefore, the disclosure that PRO mRNA is differentially expressed in normal tissue as compared to tumor tissue does not impute a specific and substantial utility to the PRO polypeptide. Based on the present disclosure,

one skilled in the art would be required to carry out further research to identify or reasonably confirm a ''real world'' context of use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a ''real world'' context of use are not substantial utilities. Thus, the present disclosure is simply a starting point for further research and investigation into potential practical uses of the claimed polypeptides. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), wherein the court held that: ''The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility'', ''[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Applicant to engross what may prove to be a broad filed'', and ''a patent is not a hunting license'', ''[i]t is not a reward for the search, but compensation for its successful conclusion.'' Applicants argue that the data in Example 18 and the first Grimaldi declaration are sufficient to establish the asserted diagnostic utility, and the office has not rebutted the presumption of utility afforded Applicants' application. Applicants argue that the first Grimaldi declaration provides further facts relating to Example 18, in that the DNA libraries used in the gene expression studies were made from pooled samples. Applicants argue that the PTO has not supplied any reasons or evidence to question the first Grimaldi declaration. Applicants remind the examiner that Office personnel must accept an opinion from a qualified expert. Applicants' arguments have been fully considered but they are not persuasive. The MPEP makes clear, "factual evidence is preferable to opinion testimony . . . .'' The MPEP also makes clear, "opinion'' testimony is entitled to be considered, i.e., it is "admissible''in an ex parte proceeding. MPEP 716.01(c). The mere fact that opinion testimony is admissible (i.e., is entitled to be considered) does not per se mean it must be accorded controlling weight. In assessing the weight to be given expert testimony in an ex parte context, the examiner may properly consider, among other things: (1) The nature of the fact sought to be established. (2) The

strength of any opposing evidence. (3) The interest of the expert in the outcome of the case. (4) The presence or absence of factual support for the expert's opinion. Unless an "expert'' states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight. The first Grimaldi declaration has been considered. However, the assertions that data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual'' (paragraph 5), "it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA'' (paragraph 6), "The precise levels of gene expression are irrelevant'' (paragraph 7), and "If a difference is detected, . . . the gene and its corresponding polypeptide . . . are useful for diagnostic purposes'' (paragraph 7) are conclusory and unsupported and rebutted by the art of record. Although the declaration states that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues, this statement is in contrast to the specification's teachings, which discloses " Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor." Page 140, paragraph 0530. It is unknown what level of difference is being reported or how many samples were tested. The declaration does not provide anything specific concerning PRO mRNA expression, PRO polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. Given the paucity of information regarding PRO mRNA expression and the complete lack of data concerning PRO polypeptide expression, Hu and LaBaer are evidence that a skilled artisan would consider the precise level of PRO gene expression as relevant. The asserted diagnostic utility of the PRO polypeptide depends upon its ability to differentiate normal tissue and

tumor tissue. In practicing the invention some value for PRO polypeptide expression must be obtained in order to make this distinction. Establishing a cutoff value for this distinction would be difficult unless one knows the degree of variation within the pool, which Applicants have not prodded. There is no evidence of record concerning the normal range of PRO mRNA levels or PRO polypeptide levels in normal tissue or tumor tissue. There is no evidence of record that a normal range of PRO mRNA or PRO polypeptide levels could be defined that would distinguish normal tissue and tumor tissue. Without any knowledge of the variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue. Pooled samples would also obscure the variation between samples, making the disclosed results for PRO polynucleotide expression less useful, accurate and informative than if results from individual samples had been provided. In fact the range of values from normal and/or tumor tissue could be so broad that it would be impossible to distinguish normal tissue from tumor tissue. As such, the Grimaldi declaration has been properly disposed of and is not persuasive in view of the countervailing evidence of record.

Applicants argue that it is the microarray assays that are inaccurate and instead rely on a more accurate and reliable method of assessing changes in mRNA levels, namely quantitative PCR analysis. The accuracy of the method of detecting the mRNA level does not cure the deficiency of the teachings of the specification as to points (1) or (2) above. Applicants argue Kuo et al that there is a good correlation between mRNA levels and protein levels when the mRNA is measured by quantitative PCR analysis. This is not persuasive; the quantitative levels have not been reported in the specification. Further, the studies of Kuo et al differ from the instant situation, because they compare within the same cell, whereas in the instant case, two different cells are compared. There is no evidence of tumor-dependent versus tumor-independent changes. Hu's statement are relevant because the specification is relying on a presumption of tumor-dependent changes and a correlation of mRNA levels with protein levels. Applicants essentially argue that

because the PCR analysis is more sensitive at the mRNA level.. then it necessarily follows that protein levels are corresponding. This is not persuasive; the ability to have a more sensitive detection in changes at the mRNA level does not establish that the change is tumor-dependent or that the protein is correspondingly changed. Applicants again argue the reasonable correlation standard. This is again not persuasive, in view of the countervailing art of record as discussed above.

Applicants argue that it is inappropriate to require statistical certainty because the appropriate standard is "more likely than not true.'' and cite *Nelson V. Bolwer*, 626, F.2d 853, 206, USPQ 881 (CCPA) to establish that any pharmacological activity that is reasonably indicative of the desired response is sufficient to establish practical utility. Applicants' arguments have been fully considered but they are not persuasive. There is no assay in the instant specification that provides for a pharmacologic activity of the polypeptide. There is no functional assay for the function of the polypeptide. The polypeptide is not characterized and no functions are described. Unlike a situation wherein the specification discloses that receptor A is present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells, in the present case Applicants rely on a qualitative comparison of PRO mRNA expression between tumor tissue and normal samples in order to establish utility for the presently claimed polypeptides. However, Applicants have not looked at whether the reported change in the transcript level for the gene leads to a change in the level of expression of the PRO polypeptide. Furthermore, a skilled artisan would not know if the reported change in PRO transcripts is disease-dependent or disease-independent. Even if the office were to assume that the change in PRO mRNA transcripts could reasonably be correlated with an assumed change in PRO polypeptide expression, it still could not be ascertained if the assumed change in PRO polypeptide expression would be disease-dependent or disease-independent because the skilled artisan would not know if the change in PRO transcripts is disease-dependent or disease-independent. The specification lacks a sufficient correlation between the test

performed on PRO transcripts and the asserted utility of the PRO polypeptide. Because Applicants have failed to establish any correlation between PRO mRNA expression and PRO polypeptide expression in normal tissue or tumor tissue Applicants have failed to establish a significant probability that PRO polypeptide is useful as a cancer diagnostic or therapeutic. There is no reason for the skilled artisan to believe that it is more likely than not that the claimed polypeptides could be used as a cancer diagnostic or therapeutic. Applicants argues Example 18 and indicates that the challenge to the sufficiency of the data is inappropriate. Applicants are the ones arguing that the first Grimaldi declaration establishes that the data in Example 18 are reproducible, reliable, and significant enough. There is no evidence of record that the data in Example 18 are consistent, reproducible, or reliable. Although the reported change in PRO mRNA may be significant, it is unknown what level of difference is being reported and whether these changes are tumor-dependent or tumor-independent. It is completely unknown and not predictably how to apply the results of qualitative mRNA levels in Example 18 to the claimed polypeptides for reasons of record.

Applicants argue that they assert a change in mRNA levels is reflected in a change of protein levels and rely on a plethora of references to show, where actually studied that there is a corresponding change. This is not persuasive for reasons of record. Hu and LaBaer developed MedGene as a means for evaluating and validating large data sets of gene expression data. MedGene is not limited to any specific relationship type, but rather encompasses all reported gene-disease links. See LeBaer, page 977, leftmost column. Bias or no bias, a gene whose change in expression is attributable to disease-independent differences between the samples cannot be used as a diagnostic indicator of the disease. Although Hu indicates that the observed correlation was only found among ER-positive tumors, not ER-negative, Hu's approach identified a set of relatively understudied, yet highly expressed genes in ER-negative tumors that are worthy of further examination. This is consistent with Hu's conclusion that even when expression changes as small as 2-

fold are statistically significant, it is not always clear if they are biologically meaningful. These small changes in expression may reflect genes whose role in cancer may not involve large changes in expression or genes whose modest changes in expression may be unrelated to the disease. The alleged bias does not vitiate the finding that mRNA or protein changes of as little as two-fold are not uncommon, and although some changes of this magnitude turn out to be important, *most are attributable to disease-independent differences between the samples*. There is no evidence of record that PRO transcripts are either highly expressed or highly under-expressed or that the reported change in PRO transcripts is consistent, reliable and measurable. There is a total lack of data concerning PRO polypeptide expression. Applicants argue that references such as Hu, Chen et al, Anderson et al etc are not relevant to the present application, which does not rely on microarray data. Applicants argue that the microarray technique is not as accurate as the RT-PCR method used by Applicants. Applicants' arguments have been fully considered but they are not persuasive because they are conclusory and unsupported and do not obviate the issues with respect to correlation with protein levels and tumor-dependent versus tumor-independent changes. The examiner has addressed Applicants' comments regarding the accuracy of pooled samples, above. Applicants argue that genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. Applicants' arguments have been fully considered but they are not persuasive. Applicants have not provided any evidence that the observed change in PRO transcripts are reliable, consistent or reproducible. The office does not and has not asserted or required that one must know what role a gene or polypeptide plays in cancer for it to have utility. The examiner did assert that the specification does not provide any information regarding the expression, role, or activity of the polypeptide in cancer. Applicants argue that neither Haynes nor Gygi looked at whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Applicants argue that

Haynes and Gygi are irrelevant to Applicants' assertions. Applicants argue that the office's interpretation is inconsistent with Haynes and Gygi. Applicants argue that neither Haynes nor Gygi address Applicants' assertion that generally, changes in mRNA level for a particular gene lead to changes in the level of the encoded protein. Applicants' arguments have been fully considered but they are not persuasive. Applicants have not examined whether the reported change in PRO transcripts is correlated with a corresponding change in PRO polypeptide expression. It is further noted that Applicants' differential analysis is based upon comparing the steady-state levels of PRO transcripts in one or more normal tissues with the steady state levels of PRO transcripts in one or more tumor tissues. See the specification at page 140, paragraph 0530: Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. Applicants assume that transcript levels are indicative PRO polypeptide levels. The specification fails to provide any testing of PRO polypeptide levels. Haynes teaches "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis'' (page 1863, right column, paragraph 2). "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts.'' Page 1870 left column, last 111 paragraph; Because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis the skilled artisan would not know if the disclosed change in PRO mRNA transcripts is associated with a corresponding change in the level of PRO protein. Hence, the skilled artisan would not know

if or how PRO polypeptide expression would change in cancer. This conclusion is supported by Allman (Blood. 1996 Jun 15;87412):5257-68), Molecular Biology of the Cell, 3rd ed., Molecular Biology of the Cell, 4th ed., Genes V1 , the Polakis declaration, and Meric (Mol Cancer Ther. 2002 Sep;1(1 1):97 1-9), as discussed above. The poor correlation of mRNA expression in cancer proteomics is known in the art and reiterated by Gronborg et al (Molecular and Cellular Proteomics, 2006 Abstract only) which teaches that the protein expression data using stable isotope labeling with amino acids in cell culture were compared to mRNA expression data obtained using gene expression microarrays and a correlation coefficient (r) of 0.28 was obtained, confirming previously reported poor associations between RNA and protein expression profiles. If one is to argue, as Applicant has argued, that because PRO transcripts are differentially expressed in tumors it is more likely than not that the PRO polypeptide is similarly differentially expressed in tumors, and therefore the PRO polypeptide and if one is to argue, as Applicants have argued, that because PRO transcripts are antibodies can be used for tumor diagnosis, then one must also accept the argument that because resting B cells and germinal center B cells express similar BCL-6 mRNA levels it is more likely than not that the BCL-6 protein is not differentially expressed in these two cell populations, and therefore the BCL-6 protein and antibodies thereto cannot be used as a marker for germinal center B cells. One must also accept the argument that because germinal center B-cells express dramatically more BCL-6 protein than resting B cells it is more likely than not that BCL-6 mRNA is differentially expressed in these two cell populations, and therefore BCL-6 mRNA can be used as a marker for germinal center B-cells. Allman indicates that this is not so. The fact that it was unexpected that increases in BCL-6 protein were not correlated with a corresponding change in the level of BCL-6 mRNA only establishes that the skilled artisan would not know if or how PRO polypeptide expression changes in tumors. Unlike Allman, Applicants have not provided any testing of the role, activity or expression of the PRO polypeptide. Applicants argue that they have established that the accepted understanding

in the art is that there is a reasonable correlation between the level of mRNA and the level of the encoded protein. Applicants argue that it is well established that a change in the level of mRNA generally leads to a change in the level of the corresponding protein. Applicants argue that the second Grimaldi declaration and the Polakis declaration, as supported by Molecular Biology of the Cell, 3rd ed., Molecular Biology of the Cell, 4th ed., as further supported by Genes VI, and as additionally supported by Zhigang and Meric , establish that there is a positive correlation between changes in mRNA levels and changes in the corresponding protein levels. Applicants' arguments have been fully considered but they are not persuasive. Applicants assume that the reported change in PRO mRNA transcripts is associated with a corresponding change in PRO polypeptide expression. Haynes, Allman, the Polakis declaration, Molecular Biology of the Cell, 3rd ed., Molecular Biology of the Cell, 4th ed., Genes VI, and Meric are evidence that the skilled artisan would not know if or how PRO polypeptide levels would change in tumors', as discussed above. The second Grimaldi declaration has been considered. The MPEP makes clear, "factual evidence is preferable to opinion testimony . . . .'' The MPEP also makes clear, "opinion'' testimony is entitled to be considered, i.e., it is "admissible'' in an ex parte proceeding. MPEP j716.01(c). The mere fact that opinion testimony is admissible (i.e., is entitled to be considered) does not per se mean it must be accorded controlling weight. In assessing the weight to be given expert testimony in an ex parte context, the examiner may properly consider, among other things: (1) The nature of the fact sought to be established. (2) The strength of any opposing evidence. (3) The interest of the expert in the outcome of the case. (4) The presence or absence of factual support for the expert's opinion. Unless an "expert'' states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight. The facts to be established are whether or not the disclosed change in PRO transcripts is disease-dependent or disease-independent and whether or not there is a positive correlation between the reported

change in PRO transcripts and a change in PRO polypeptides levels in tumors as compared to their normal tissue counterparts. In the present case it is unknown if the reported change in PRO mRNA expression is tumor-dependent or tumor-independent. The declaration does not provide any data concerning PRO mRNA expression, PRO polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO transcripts and PRO polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the Polakis declaration. The assertion that PRO polypeptide expression is useful regardless of the correlation between PRO mRNA expression and PRO polypeptide expression because it would allow more accurate tumor classification is akin to asserting that whatever the expression level and whatever the correlation, the PRO polypeptide and antibodies are useful because skilled artisans could figure out for themselves what any observed experimental result might mean. The specification does not disclose anything regarding "more accurate tumor classification.'' The examiner does not agree that such a disclosure provides a "specific benefit in currently available form'' because the expression of all polynucleotides or polypeptides from a tumor sample can invariably be classified as either increased, decreased, non-existent or unchanged as compared to some standard level of expression. It can then be asserted that all proteins or polynucleotides that are expressed in this manner can be used to detect, characterize or classify the tumor. Such an asserted utility is not specific to the PRO gene or polypeptide and is analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility. Unlike the situation in Grimaldi (Blood. 1989 Jun;73(8):2081-5), wherein chromosomal translocations have proven to be important markers of the genetic abnormalities central to the pathogenesis of cancer, there is no evidence that the

present situation involves the cloning of a chromosomal breakpoint. Unlike Wang et al, Manaut et al Hui et al, Khal et al, Maruyama et al, Caberlotto et al, Meeker (pages 12-18) and the 113 other references. Applicants have not provided any testing of the level of expression, activity, or role in cancer of the PRO polypeptide. The examiner has already responded to Applicants' arguments regarding the caveat in the Example 12 of the utility guidelines, above. The Polakis declaration has also been considered. The MPEP makes clear, "factual evidence is preferable to opinion testimony . . . .'' The MPEP also makes clear, "opinion'' testimony is entitled to be considered, i.e., it is "admissible'' in an ex parte proceeding. MPEP 716.01(c). The mere fact that opinion testimony is admissible (i.e., is entitled to be considered) does not per se mean it must be accorded controlling weight. In assessing the weight to be given expert testimony in an ex parte context, the examiner may properly consider, among other things: (1) The nature of the fact sought to be established. (2) The strength of any opposing evidence. (3) The interest of the expert in the outcome of the cue. (4) The presence or absence of factual support for the expert's opinion. Unless an "expert'' states the underlying basis for an opinion, it may be difficult to accord the opinion significant weight. Opinions expressed without disclosing the underlying facts or data may be given little, or no, weight. The facts to be established are whether or not the disclosed change in PRO transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO transcripts and a corresponding change in PRO polypeptides levels. The declaration does not provide any data concerning PRO mRNA expression, PRO polypeptide expression, or the correlation between the two in tumor tissue or normal tissue. Given the paucity of information regarding PRO expression in tumors and the evidence in the art that there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis, one skilled in the art would not know if the change in PRO mRNA expression was disease-dependent or disease-independent, would not know if or how polypeptide expression would change in tumors, and would have a

reasonable, legitimate basis to doubt the utility of the PRO polypeptide. Even if the examiner were to assume that the disclosed change in PRO transcripts could reasonably be correlated with an assumed change in PRO polypeptide expression, it still could not be ascertained if the assumed change in PRO polypeptide expression would be disease-dependent or disease-independent because it is unknown if the change in PRO transcripts is disease-dependent or disease-independent. While Dr. Polakis refers to his experiments, only conclusions were set forth in the declaration. No data or results were presented for independent analysis. Even if the examiner were to accept Dr. Polakis' conclusion, it still would be considered evidence that the skilled artisan would not know if or how PRO polypeptide expression would change in cancer because 20% of the cases examined do not show a correlation, according to Dr. Polakis. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO transcripts and PRO polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to Dr. Polakis. Applicants emphaize that they do not need to prove an exact or absolute correlation between changes in mRNA and changes in protein levels. Applicants' arguments have been fully considered but they are not persuasive. The examiner considers these arguments somewhat misleading because Applicants have never been asked prove such an exact or absolute correlation. Nor have Applicants been required to establish the asserted diagnostic utility as a matter of absolute or statistical certainty, as discussed above. Rather, the facts to be established are whether or not the disclosed change in mRNA transcripts is disease-dependent or disease-independent and whether or not there is a correlation between the reported change in PRO transcripts and a corresponding change in PRO polypeptides levels. Molecular Biology of the Cell, Genes VI, Zhigang, and Meric are acknowledged. However, Molecular Biology of the Cell

acknowledges that "other controls can act later in the pathway from DNA to protein to modulate the amount of gene product that is made'' (page 453, last full paragraph). Molecular Biology of the Cell acknowledges that the final level of protein depends upon the efficiency with which each of the many steps from DNA to protein is performed (page 363, last full paragraph and page 364, Figure 6-90). Genes VI acknowledges that "the production of RNA cannot inevitably be equated with production of protein'' (paragraph bridging pages 847-848). Molecular Biology of the Cell and Genes VI support and are consistent with the office's position that the skilled artisan would not know if or how PRO polypeptide expression would change in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The examiner does not agree that Figure 6-3, page 302 illustrates a basic principle that there is a correlation between increased gene expression and increased protein expression. This figure only illustrates that different genes can be expressed with different efficiencies. Regarding Zhigang , Applicants argue that statistical certainty is not a requirement, and that the PTO is requiring statistical certainty. Applicant's arguments have been fully considered but they are not persuasive. It is acknowledged that Zhigang presents data showing a high degree of correlation between PSCA protein and mRNA expression (page 4 of 7, right column, last sentence). However, exceptions were noted (paragraph bridging pages 3 of 7 and 4 of 7) page 4 of 7, left column, full paragraph 1). Thus, Zhigang supports and is consistent with the examiner's position that the skilled artisan would not know if or how PRO polypeptide expression would change in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The examiner is not requiring statistical certainty. Unlike Zhigang, Applicants have not provided any testing of the PRO polypeptide. Zhigang does not provide any data concerning PRO mRNA expression, PRO polypeptide expression,

or the correlation between the two in tumor tissue or normal tissue. The fact that there may be a general correlation does not tell the skilled artisan if the reported change in PRO transcripts is disease-dependent or disease-independent and does not tell the skilled artisan if or how PRO polypeptide expression changes. Regarding Meric, Applicants do not assert that transcriptional levels are the only factor in determining polypeptide levels. Applicants assert that changes in mRNA levels are generally indicative of changes in polypeptide levels. Applicant's arguments have been fully considered but they are not persuasive. Meric states that the "fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells'' (page 971, right column, first paragraph of "Introduction''). However, the present specification does not provide any testing of the level of expression, activity, or role in cancer of the PRO polypeptide. Therefore, the difference in PRO polypeptide expression between cancer cells and normal cells is unknown, and thus not exploitable. Meric also acknowledges that several alterations in translational control occur in cancer (page 971, Abstract) and that gene expression is quite complicated (page 971, right column, first paragraph of "Introduction''), suggesting that protein levels can be modulated independently of the level of mRNA. Thus, Meric supports and is consistent with the examiner's position that the skilled artisan would not know if or how 1+0874 polypeptide expression would change in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the invention. The fact that one of skill in the art can potentially exploit the differences in gene expression between cancer cells and normal cells does not tell the skilled artisan if the reported change in PRO transcripts is disease-dependent or disease-independent and does not tell the skilled artisan if or how PRO polypeptide expression changes in tumor tissue.

The examiner has already responded to Applicants' discussion of the utility legal

standard, burden of proof and standard of proof above. Applicants' conclusion regarding the utility of the claimed invention has been considered but it is not persuasive. In the present case, the differential analysis of PRO transcripts does not prove that the PRO polypeptide will perform as a cancer diagnostic or therapeutic. The differential expression of the PRO polynucleotide has not been adequately correlated with the contemplated cancer diagnostics or therapeutics of the PRO polypeptide or antibodies. The PRO polynucleotide and polypeptide have not been tested to the extent that utility would be known to those of skill in the art.

Claims 6-17 also stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention is maintained for reasons made of record in the Office Action mailed 1-27-06 and herein.

Claims 14-17 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons made of record in all the previous Office Actions of record.

Applicants' arguments have been carefully considered but are again not persuasive. Applicants argue that given the now inserted functional limitation that the rejection should be dropped because the genus is not vast. This is not persuasive, the genus is vast and the issue with respect to amino acid changes affecting antibody binding as set forth in the previous office action have not been addressed. Applicants argue that the examiner has not provided any reasoning or evidence as to how the absence of the disclosure of a biological activity results in a lack of written description. Applicants argue that there is no substantial variation within the genus and that Applicants were in possession of the

common attributes or features of the claimed invention. Applicants argue that the claims are analogous to Example 14 of the written description guidelines because it was well known in the art how to make polypeptides having the recited percent identity, as evidenced by the specification at paragraphs 0256-0271, and because the specification discloses how to make antibodies that detect a particular PRO polypeptide and how to use them, as evidenced by the specification at paragraphs 0363-0379, 0407 and 0493-0499. Applicants argue that the function of producing an antibody specific to SEQ ID N0:46 is directly related to the structure of the claimed polypeptides. Applicants argue that Example of the written description guidelines extends to all situations where the polypeptide is useful and there is no substantial variation within the genus. Applicants argue that claims 14-17 must share a particular biologic activity that restricts the amount of permissible structural variation within the genus. Applicants argue that the premise that a large genus cannot be described by a single species is wrong. Applicants argue that the facts in *Wallach* are very similar to the present case. Applicants argue that it is routine to make the claimed variant polypeptides and is just as predictable and easy as creating all the nucleic acid molecules that encode a particular amino acid sequence. Applicants argue that it well within the purview of skilled artisans to determine which polypeptides can be used to make the recited antibodies. Applicants argue that the predictability of this structure/function combination is sufficient to put Applicants in possession of the claimed invention. Applicants' arguments have been fully considered but they are not persuasive. The claims are not drawn to nucleic acids encoding the same protein, the claims are drawn to different proteins having different structures. Applicants reliance on *Wallach* is therefore misplaced. The specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO, as indicated below: ''Active'' or ''activity'' for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein ''biological'' activity refers to a biological

function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an ''immunological'' activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO. Page 39, paragraph 0231. Therefore, the claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity to the amino acid sequence of SEQ ID NO:46, and possessing any and/or all underlying biological activities. However, the specification does not describe any biological activity of the native or naturally-occurring PRO polypeptide SEQ ID N0:46. The office disagrees with the premise that making the claimed variant polypeptides and is just as predictable and easy as creating all the nucleic acid molecules that encode a particular amino acid sequence. All nucleic acid molecules that encode a particular amino acid sequence all share the same property of encoding that amino acid sequence. The nature, type and number of nucleotide changes are discernable and predictable. However, the claimed variant polypeptides are all different polypeptides. The claims encompass polypeptides that vary anywhere and everywhere from SEQ ID N0:46, within the metes and bounds of the recited percent identity. Note that the claims are not limited to fusion proteins. Unlike a biological activity, which imposes limitations on the nature, type and number of amino acid changes, the functional property of "can be used to generate an antibody . . . to specially detect the polypeptide of SEQ ID N0:46'' does not limit the variation in the structure SEQ ID N0:46 - the structure of the claimed variants - in any discernable, predictable or disclosed manner. Because the specification does not describe any biological activity of the claimed polypeptides and because the claims are not limited to any specific biologic activity of the claimed polypeptides, the present claims are not analogous to the Example of the written description guidelines. Furthermore, an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:46 in stomach or skin tissue samples is essential to applicants' claimed genus of variant polypeptides. The

specification defines antibody specificity as follows: An antibody that ''specifically binds to'' or is ''specific for'' a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247. The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The obvious choice is to use the polypeptide itself. Therefore, the function of the claimed variants is not related to the structure of the claimed variants. After reading the specification, a person of skill in the art would not understand Applicants to have invented a polypeptide having the recited percent identity that can be used to make an antibody which can be used to specifically detect the polypeptide of SEQ ID N0:46, except for the native naturally occurring PR0 polypeptide (SEQ ID N0:46). Skilled artisans would not recognize the disclosure of SEQ ID N0:46 as putting Applicants in possession of the claimed genus. Applicants separately argue that claim 15 is adequately described for the same reasons that claims 14, 16, and 17 are adequately described. Applicants further argue that because the genus of polypeptides is smaller than that of claim 14 the board should reverse the rejection of claim 15. Applicants' arguments have been fully considered but they are not persuasive. Claim 15 is not adequately described for the same reasons claim 14 is not adequately described, as discussed above. Although the polypeptides of claim 15 are 99% identical to SEQ ID NO:46, the specification does not describe any biological activity of the native or naturally-occurring PR0 polypeptide or any variant thereof. Furthermore, the state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. Applicants argue the Sutcliff abstract. It is noted that Sutcliff et al has no bearing on variants of polypeptide, but merely discusses using peptide fragments of a specific polypeptide as immunogens for generating antibodies with predefined specificity to the same polypeptide from which the peptide fragment is

derived. This application is not claiming peptide immunogens or fragments of a particular protein that are used to generate antibodies to the same but larger polypeptide. Moreover, the skilled artisan cannot follow Sutcliff's simple rules, because the other variants are not described in this specification and therefore how would one skilled in the art determine a ***conserved*** small peptide to be synthesized to make an antibody with a defined reactivity to the substantially larger SEQ ID NO:46. Simply put, Applicants were not in possession of the variants and therefore the skilled artisan would not be readily apprised of what subsequence of the non-described, non-disclosed variant(s) to use as a peptide immunogens according to Sutcliff's alleged "rules". The skilled artisan would not know if the peptide selected from an randomly generated variant produced an antibody that did not bind SEQ ID NO:46. The antibody binding specificity is determined by the immunogen and variances in the amino acid structure affects antibody binding (see the Office Action mailed 1-27-06). Skilled artisans would not recognize the disclosure of SEQ ID NO:46 as putting applicants in possession of the claimed genus. In the instant case, while the skilled artisan may envision may changes to the polypeptide, one can not envision what changes to the structure or what part of the structure is conserved as it correlates with the now claimed properties. The immunological equivalent variants are not provided by disclosure of a single polypeptide because it is well established in the art the retention of specificity following one or more amino acid substitutions in a polypeptide is another factor that has been shown to be unpredictable in the art. For instance, McGuinness *et al.* (*Mol. Microbiol.* 7: 505-514, Feb 1993) taught that "[a] single amino acid change within an epitope, or an amino acid deletion outside an epitope, were both associated with loss of subtype specificity resulting from a change in the predicted conformation at the apex of the loop structure" in case of a meningococcal polypeptide (see abstract). Similarly, McGuinness *et al.* (*Lancet* 337: 514-517, March 1991) taught that a point mutation generating a single amino acid change in a P1.16-specific epitope in the VR2 region of the *porA* gene of a strain of *Neisseria meningitidis* of subtype P1.7,16 resulted in "striking

changes in the structural and immunological properties of the class 1 protein" of this isolate (see abstract and page 514). Additionally, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986) taught the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24): "One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool." The specification as filed does not provide written description of a representative number of variants retaining the ability to gnereat antibodies that specifically detect as claimed. Thus, Applicant was not reasonably in possession of the "claimed genus of polypeptides" encoded by a genus of polypeptides to raise antibodies that bind a different polypeptide for the reasons previously made of record and herein.

Claims 6 and 11-17 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons made of record in the Office Action mailed 3-24-05 and maintained 1-27-06.

Applicants indicate that a "statement containing the information requested has been provided. However, the response was not apparently accompanied by such a statement or it is not scanned and there is no apparent copy of a substitute statement or substitute declaration in the IFW prosecution record.

Claims 14-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons made of record in the Office Action mailed 1-27-06.

As to claims 14-17, Applicants' arguments have been carefully considered but are not persuasive. Claims 14-17 recite the limitation wherein said polypeptide . . . can be used to generate an antibody . . . .'' These claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity, regardless of the biological activity. Applicants have not described the biologic activity of the PRO polypeptide or any of its variants. It is entirely unclear why the disclosure of a single polypeptide, i.e., the Pro polypeptide of SEQ I DNO:46, which is ideally suited to the making of antibodies to itself, would describe any and all antigenically cross-reactive polypeptides possessing the recited percent identity and possessing unknown and undisclosed biologic activities, when the specification does not describe any biological activity. Therefore, the claimed subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors), at the time the application was filed, had possession of the claimed invention. Applicants argue that the examiner has not provided any reasoning or evidence as to how the absence of the disclosure of a biological activity results in a lack of written description. Applicants argue that there is no substantial variation within the genus and that Applicants were in possession of the common attributes or features of the claimed invention. Applicants argue that the claims are analogous to Example 14 of the written description guidelines because it was well known in the art how to make polypeptides having the recited percent identity, as evidenced by the specification at paragraphs 0256-0271, and because the specification discloses how to make antibodies that detect a particular PRO polypeptide and how to use them, as evidenced by the specification at paragraphs 0363-0379, 0407 and 0493-0499. Applicants argue that the function of producing an antibody specific to SEQ ID N0:46 is directly related to the structure of the claimed polypeptides. Applicants argue that

Example of the written description guidelines extends to all situations where the polypeptide is useful and there is no substantial variation within the genus. Applicants argue that claims 14-17 must share a particular biologic activity that restricts the amount of permissible structural variation within the genus. Applicants argue that the premise that a large genus cannot be described by a single species is wrong. Applicants argue that the facts in *Wallach* are very similar to the present case. Applicants argue that it is routine to make the claimed variant polypeptides and is just as predictable and easy as creating all the nucleic acid molecules that encode a particular amino acid sequence. Applicants argue that it well within the purview of skilled artisans to determine which polypeptides can be used to make the recited antibodies. Applicants argue that the predictability of this structure/function combination is sufficient to put Applicants in possession of the claimed invention. Applicants' arguments have been fully considered but they are not persuasive. The specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO, as indicated below: ''Active'' or ''activity'' for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein ''biological'' activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and an ''immunological'' activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO. Page 39, paragraph 0231. Therefore, the claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity to the amino acid sequence of SEQ ID NO:46, and possessing any and/or all underlying biological activities. However, the specification does not describe any biological activity of the native or naturally-occurring PRO polypeptide SEQ ID NO:46. The office disagrees with the premise that making the claimed variant polypeptides and is just as predictable

and easy as creating all the nucleic acid molecules that encode a particular amino acid sequence. All nucleic acid molecules that encode a particular amino acid sequence all share the same property of encoding that amino acid sequence. The nature, type and number of nucleotide changes are discernable and predictable. However, the claimed variant polypeptides are all different polypeptides. The claims encompass polypeptides that vary anywhere and everywhere from SEQ ID N0:46, within the metes and bounds of the recited percent identity. Note that the claims are not limited to fusion proteins. Unlike a biological activity, which imposes limitations on the nature, type and number of amino acid changes, the functional property of "can be used to generate an antibody . . . to specially detect the polypeptide of SEQ ID N0:46'' does not limit the variation in the structure SEQ ID N0:46 - the structure of the claimed variants - in any discernable, predictable or disclosed manner. Because the specification does not describe any biological activity of the claimed polypeptides and because the claims are not limited to any specific biologic activity of the claimed polypeptides, the present claims are not analogous to the Example of the written description guidelines. Furthermore, an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:46 in stomach or skin tissue samples is essential to applicants' claimed genus of variant polypeptides. The specification defines antibody specificity as follows: An antibody that ''specifically binds to'' or is ''specific for'' a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247. The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The obvious choice is to use the polypeptide itself. Therefore, the function of the claimed variants is not related to the structure of the claimed variants. After reading the specification, a person of skill in the art would not understand Applicants to have invented a polypeptide having the recited percent identity that can be used to make an antibody

which can be used to specifically detect the polypeptide of SEQ ID NO:46, except for the native naturally occurring PRO polypeptide (SEQ ID NO:46). Skilled artisans would not recognize the disclosure of SEQ ID NO:46 as putting Applicants in possession of the claimed genus. Applicants separately argue that claim 15 is adequately described for the same reasons that claims 14, 16, and 17 are adequately described. Applicants further argue that because the genus of polypeptides is smaller than that of claim 14 the board should reverse the rejection of claim 15. Applicants' arguments have been fully considered but they are not persuasive. Claim 15 is not adequately described for the same reasons claim 14 is not adequately described, as discussed above. Although the polypeptides of claim 15 are 99% identical to SEQ ID NO:46, the specification does not describe any biological activity of the native or naturally-occurring PRO polypeptide or any variant thereof. Furthermore, the state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. Skilled artisans would not recognize the disclosure of SEQ ID NO:46 as putting applicants in possession of the claimed genus.

Claims 6, 8, 10 and 12-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons made of record in the Office Action mailed 1-27-06.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that the metes and bounds of the signal peptide are set forth in Figure 46 of the specification. It is noted that while the claims are read in light of the specification, specific limitations from the specification or figures are not read into the claims. Not all peptides have the identical signal sequence and the claims do not identify the metes and bounds of the signal sequence. The claims are *prima facie* indefinite because the claims no longer define the metes and bounds of the signal peptide as was

previously referenced by specific reference to the figure in the claims. Consequently, the skilled artisan would not be readily apprised of the length of the polypeptide and would not be able to readily ascertain if they were in possession of the claimed in invention.

Claims 6, 9, 10, 12-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons made of record in the Office Action mailed 1-27-06.

Applicants' arguments have been carefully considered but are not persuasive. Applicant relies solely on the description of Figure 46 to infer an extracelluar domain. This is not persuasive; the term "extracellular" explicitly indicates that the region falls outside of the cell. The provision of "extracellular" domain or region does not have support in Figure 46 as filed. While the figure teaches transmembrane domains, there is no indication that the referenced membrane is the cellular membrane as opposed to the nuclear, mitochondrial, golgi or any other intracellular membrane. As such, the positioning of the intervening sequence of residues 23-223 could not necessarily be interpreted as "extracellular" as now recited. Therefore, in view of the lack of explict support or implicit support for the now recited metes and bounds of the extracellular domain as discussed supra, this limitation is deemed new matter. Applicants argue that the specification contemplates fragments that have the transmembrane deleted as contemplated at paragraph [0017]. This does not provide support for extracelluar because the recitation of transmembrane does not point one skilled in the art to what particular membrane and does not include intracellular membranes. The concept of a deletion mutant of a particularly defined region (transmembrane) does not proved implicit or explict support for other domains. Applicants also point to [0014] that teach a variety of fragments. This is not persuasive, the passage provides for fragments as specifically disclosed herein. Figure 46 only discloses and names signal peptide residues 1-22, transmembrane domain amino acids 224-250, leucine zipper pattern amino acid residues

229-251 and N-glycosylation sites. Applicants in particular rely upon "any other specifically defined fragment" littered throughout the specification. It is the position of the office that the only specifically defined fragments of Figure 46 are those recited therein. The specification does not explicitly define the claimed residues as a fragment of interest, nor does it particularly describe the residues as "extracellular". Furthermore, the inference that the metes and bounds of any particularly disclosed fragment is at the boundaries between two different fragments flies in the face of the particularly set forth N-glycosylation sites and the specification which teaches that the metes and bounds of any extracelluar domain can vary (see paragraph [0197]) and therefore, the specification as filed does not explicitly or inherently point to residues 23-223 as the contemplated metes and bounds of any extracelluar domain at the time of filing.

Claims 6-7, 9, 11 and 14-15 stand rejected under 35 USC 102(b) as being anticipated by STREMBL_25, accession number Q9NY23 for reasons made of record in the Office Action mailed 3-24-05.

Applicants argue the priority date of the instant Application. In order to be accorded priority under 35 USC 120 or 119(e) the earlier filed application must comply with 35 USC 112, first paragraph. This application fails to comply with 35 USC 112, first paragraph and each of the earlier applications are similarly flawed. Priority for prior art purposes to the earlier filed applications is denied and the art rejection stands for reasons made of record.

Claims 6-17 stand rejected under 35 USC 102(b) as being anticipated by Khodadoust WO 99/67387, published December 29, 1999.

Khodadoust et al teach a polypeptide human myocardium protein (MP-7) represented by SEQ ID NO:2 which is 100% identical as compared to the instantly claimed SEQ ID NO:46 and residues 22-223 of SEQ ID NO:46 and as such anticipates claims 1-7,

9 and 11 on this basis. Khodadoust et al teach fragments of the MP-7 protein comprising Ig-like domains (i.e. the extracellular domains lacking the signal sequence) and MP-7 absent the signal sequence and optionally fused to a heterologous signal sequence or tag that facilitates purification of recombinant MP-7 (see [pages 5-7, 17, 36-39]). As such, Khodadoust et al anticipate the claimed invention.

Teaches the polypeptide of AAY44609 that is a human myocardium protein-7 of 335 residues in length which is 100% identical across residues 23-223 of SEQ ID NO:46. As such,

Status of Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy

Primary Examiner

Art Unit 1645